

REMARKS

Claims 1 – 3, 5 – 12, 17 – 19, 24 and 25 are currently pending. By Amendment filed herewith, claims 6, 8, 9 and 12 are withdrawn from consideration with reservation of all rights to pursue the subject matter of those claims in continuation and/or divisional applications claiming priority from the instant application. The instant Amendment also adds new claims 26 – 37, support for which may be found in the claims as filed and throughout the specification. Consequently, claims 1 – 3, 5, 7, 10, 11, 17 -19, and 24 – 37 remain for further consideration. Based on the Remarks below, Applicants respectfully submit that all claims stand in a condition for allowance, which action is earnestly requested.

REJECTIONS PREVIOUSLY OF RECORD

The Action rejected claims 1 – 3, 5, 7, 10, 11, 17 – 19, 24 and 25 under various statutory bases, as addressed below.

35 U.S.C. §102(b) (Ross *et al.*)

The Action has rejected claims 1-3, 5, 7, 10, 11 and 17-19 as allegedly being anticipated by Ross *et al.*, *Pain* 84: 421-428 (2000) (“Ross”). The Action has characterized Ross as disclosing methods of administering sub-analgesic amounts of morphine and oxycodone followed by an observation of a marked antinociceptive synergy. The Action concluded that “Ross *et al.* intrinsically reduces the risk associated with the administration of opioid analgesics in patients,” and reads on the cited claims. Applicants respectfully traverse.

Although the data disclosed in Ross *et al.*, in accord with the Action’s characterization, disclose the antinociceptive synergy arising from compositions comprising oxycodone and morphine, it is clear that this result was the sole investigative goal of the work. The reference provides no substantive data on the impact of the synergistic analgesic compositions on specific side effects such as respiratory depression, which impact is at the core of the invention disclosed and claimed in the instant application. Indeed, the very analgesic synergy disclosed in the Ross *et al.* reference would lead one of ordinary skill in the appropriate art to expect a concomitant

level of synergy with respect to side effects of this sort. The widely-accepted reference, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed., New York: McGraw-Hill (2001) (as attached to Amendment and Response filed with respect to office Action of 7 February 2007) unequivocally states, on page 579, in the context of the use of mixed opioid compositions to reduce the occurrence of side effects such as respiratory depression, that “for the same degree of analgesia, the same intensity of side effects will occur.” (Emphasis added.)

The disclosure of the Ross *et al.* reference, in qualitatively discussing potential mediation of CNS-related side effects observed in accord with co-administration of oxycodone and morphine, reveals a telling variation in the amelioration of side effects as a function of relative mass loading of oxycodone and morphine in the combination formulations. *See, for example*, section 3.3.2, p. 426, wherein certain CNS-related side effects were observed in animals receiving combination formulations, while other effects occurred to a lesser extent or not at all. This observation supports what must be an art-recognized principle that the occurrence and severity of CNS-related effects is correlated to dosing levels, whether the active ingredients are administered singly, or in combination. Thus, the only conclusion objectively supported by the disclosures of the reference is that some, but not all, CNS-related side effects may be diminished at certain loadings of the active ingredients. Because the reference does not disclose observations specifically directed to depression of respiration at any of the experimental doses, it is impossible to conclude that the disclosed formulations would be effective in reducing the occurrence of this specific type of effect and, at the same time, providing an analgesic effect.

The results disclosed in the instant application clearly provide an unexpected benefit from mixed-opioid compositions not predicted by the prior art. The disclosure of Ross *et al.* is directed to the foundation observation that analgesic synergy is possible with compositions comprising mixed μ - and κ -opioid agonists (*see* Fig. 4, p. 426, Col. 1). Any comments directed to possible implications on CNS-related side effects must be taken in the context of the specific effects the experimental protocols were designed to address, none of which included respiratory depression. The proof of an unexpected decrease in respiratory depression, in a synergistically analgesic mixed-opioid composition, has never been disclosed until the instant application. Thus, the instant application is the first disclosure to establish that it is possible to achieve both

analgesia and a reduction in respiratory depression with a composition of mixed μ - and κ -opioid agonists, as well as to teach at what relative mass loadings it is possible to achieve the desired clinical phenomena.

The Action, in rejecting these claims over Ross *et al.*, stated that “the method disclosed by Ross *et al.* intrinsically reduces the risk associated with the administration of opioid analgesics in patients,” further citing to disclosed dosing ratios of oxycodone to morphine. Applicants respectfully disagree. Looking at extremes of relative loading, even without considering analgesic synergy between μ - and κ -opioid agonists in the composition, as reflected in the new claims added by instant amendment, it is logical that, as a composition approaches a preponderance of one or the other opioid component, then the opportunity for synergy decreases, until the composition approaches a limit where it begins to function as if it contains only a single opioid component. Given that each of the single opioid components of the compositions as claimed could be present at low, potentially sub-analgesic levels, the clinical result would be ineffectiveness for its intended analgesic purpose. Thus, a threshold question arises: what is the minimum ratio of μ - and κ -opioid agonists necessary to achieve the primary analgesic effect? More importantly, in terms of the instant invention, is the question of at what relative component ratios is it possible to achieve both analgesia and a reduction in respiratory depression?

It is unlikely that data yet exists on where the absolute limits of composition capable of analgesic synergy lie. The disclosure of Ross *et al.* addresses where within those limits analgesically effective compositions may be formulated. However, there is nothing disclosed in the Ross *et al.* reference (or any other reference cited in the Action) on where within those extremes of composition is it possible to achieve both analgesic synergy and a reduction in respiratory depression.

Looking at the specific compositions disclosed in Ross *et al.*, the first route of administration involved intracerebroventricular (i.c.v.) delivery of the compositions directly into the test animal’s cerebrospinal fluid *via* a surgically-inserted cannula. The compositions delivered by this route are described as comprising 40 nmol of oxycodone and 15 nmol of morphine, when delivered in combination. However, Applicants point out that this particular route of administration (directly bypassing the blood/brain barrier) significantly affects any observed results from this composition and cannot be, as would be recognized by one of ordinary

skill in the relevant art, extrapolated to systemic routes of delivery. The Ross *et al.* reference specifically acknowledges this (see, for example, p. 422).

In looking at the other compositions disclosed in the reference, the relative mass loadings of oxycodone and morphine are considerably different from the instant invention. For intraperitoneal (i.p.) delivery, the single compositions disclosed comprised 571 nmol of morphine and 621 nmol of oxycodone.¹ For subcutaneous (s.c.) delivery, as referenced in the Action, compositions are described in terms of the ED₅₀ (providing half maximal response) dose determined from the individual doses of oxycodone and morphine. Figure 3 of the reference depicts the data on which the authors based this determination. The ED₅₀ result was calculated to be 2.8 mg/kg oxycodone and 8.5 mg/kg morphine. Consequently, relative mass ratios for the compositions administered to the test animals were as high as 9:1, morphine to oxycodone. These mass ratios are significantly different from those disclosed and claimed in the instant application. The significance of this difference is emphasized by the recognition in the art that CNS effects such as respiratory depression are mediated through the μ -opioid receptors, those to which morphine binds. If looked to at all for utility in diminishing CNS-related effects (counter to then art-accepted principles), the teachings of Ross *et al.* would be undesirable for such effect.

On this basis, Applicants respectfully submit that the cited reference does not adversely impact the patentability of the claims in questions and urges immediate allowance of same.

35 U.S.C. §102(b) (Smith *et al.* WO '438)

Of the claims under consideration, the Action has rejected claims 1-3, 5, 7, 10, 11, 17-19, 24 and 25 as allegedly being anticipated by Smith *et al.* Applicants respectfully traverse.

As addressed above in respect to the disclosures of the Ross *et al.* reference, the disclosure of the Smith *et al.* reference is directed solely to the analgesic synergy arising from compositions comprising mixtures of μ - and κ -opioid agonists. The reference does not disclose any objective data supporting a reduced occurrence of respiratory depression, from administration of the compositions. As also pointed out above, prior to the instant application, the accepted wisdom in the prior art was that any composition displaying an increased analgesic

¹ Although both i.p. and s.c. methods of administration are generally considered in the art to be systemic routes of delivery (in contrast to i.c.v., which route bypasses the blood/brain barrier), Applicants submit that data for s.c. formulations are far more relevant for comparison to clinical effects achieved through administration of oral dosage forms.

effect would also display an accompanying increase in undesirable side effects (including respiratory depression). A mere suggestion that it “may be possible” with the disclosed compositions to achieve both analgesia and reduced side effects falls far short of the standard necessary for a disclosure to anticipate claims directed to respiratory depression specifically. As for inherency, contrary to the assertion of the Action, the cited reference fails to disclose any data that would enable one of skill in the art to both recognize and to be able to select from among the wide range of compositions disclosed as displaying sufficient analgesic effect the specific sub-set of compositions that would also be capable of definitively reducing the occurrence of respiratory depression. Furthermore, the mass loadings of the disclosed compositions are heavily weighted toward much higher morphine:oxycodone mass ratios. These compositions are substantially different from those claimed in the instant application.

Thus, the cited reference provides no objective teaching that the disclosed compositions, in fact, result in a reduction of respiratory depression, nor do the specific compositions disclose the relative mass loadings of oxycodone and morphine capable of achieving analgesia without increasing the risk of respiratory depression. On this basis, Applicants respectfully suggest that the cited reference does not adversely impact the patentability of the claims and urges the Examiner to move the application to allowance.

35 U.S.C. §102(b) (Smith *et al.* ‘072 patent)

Of the claims under consideration, the Action has rejected claims 1-3, 5, 7, 10, 11, 17 – 19, 24 and 25 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* (‘072 patent). Applicants respectfully traverse.

As with the Smith *et al.* (WO ‘438) reference discussed immediately above (which reference is a foreign counterpart to the instant reference and, thus, shares a common disclosure), the cited reference falls far short of anticipating the instant claims. The reference’s disclosure is limited solely to the analgesic synergy between μ - and κ -opioid agonists and fails to provide any teaching establishing that the disclosed compositions are capable of reducing the occurrence of respiratory depression. Nor does the reference disclose or even suggest how to select from among the numerous compositions disclosed those that would be capable of both providing sufficient analgesic effect and a reduction in respiratory depression. On this basis, Applicants respectfully submit that the cited fails reference fails to anticipate the instant claims and requests

the examiner to withdraw the instant rejection.

35 U.S.C. §103(a) (Smith *et al.* WO '438)

Of the claims under consideration, the Action has rejected claims 1-3, 5, 7, 10, 11, 17 - 19, 24 and 25 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* (WO '438). Applicants respectfully traverse.

The Action has cited the reference on the basis that the reference allegedly motivates one of skill in the art to substitute oxymorphone for morphine in the compositions disclosed therein. Based on the instant amendment to the claims, Applicants submit that this basis of rejection has been rendered moot and request that same be withdrawn.

Objection to Drawings

The Action has indicated an objection to the drawing for Figure 1 on the basis that the legend for the ordinate axis is not legible. Applicants hereby acknowledge said objection and further indicate that, upon receipt of a Notice of Allowance for the instant application, will submit a corrected drawing addressing the noted problem.

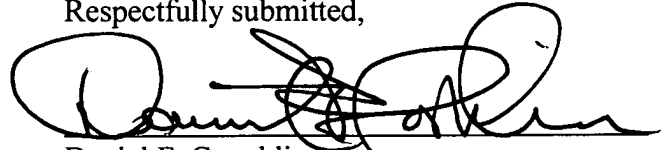
Newly Added Claims

Based on the Remarks above, and ample support for the new claims throughout the specification, Applicants respectfully submit that these claims stand in a condition for allowance, which action is earnestly requested.

Applicants authorize the charge of any deficiency and/or the credit of any overpayment to deposit account 50-1943.

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Respectfully submitted,



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